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Strain relatedness of meticillin-resistant *Staphylococcus aureus* isolates recovered from patients with repeated bacteraemia

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Abstract

Information on the relatedness of isolates causing repeated meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is limited. An observational study of 177 patients with MRSA bacteraemia, admitted to the emergency department of National Taiwan University Hospital, was conducted from January 2001 to June 2006. Among these patients, 28 had a previous episode of MRSA bacteraemia and 59 died during the index episode of bacteraemia. Until December 2007, among the 118 patients who survived the index episode (101 without previous bacteraemia and 17 with previous bacteraemia), 24 (20.3%) had repeated MRSA bacteraemia. The duration from discontinuation of antimicrobial therapy to repeat episodes was in the range 35–854 days (median 86 days). Eight patients (33.3%) died as a result of the second bacteraemic episode. Clinical characteristics associated with repeated bacteraemia included the diagnosis of infective endocarditis and active malignancy. Pulsed-field gel electrophoresis and multilocus sequence typing analysis were performed for 32 pairs of available isolates recovered from patients with repeated bacteraemia and revealed that 29 of them (90.6%) were genetically closely-related strains. The majority of patients with repeated MRSA bacteraemia had recurrent infections and a high mortality rate.

Keywords: Meticillin-resistant *Staphylococcus aureus,* outcome, recurrence, repeated bacteraemia
Original Submission: 20 October 2008; **Revised Submission:** 16 April 2009; **Accepted:** 20 April 2009
Editor: G. Lina
Article published online: 15 July 2009
Clin Microbiol Infect 2010; **16:** 463–469
10.1111/j.1469-0691.2009.02885.x

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Introduction

Because of advances in patient care and the pathogen's ability to adapt to a changing environment, the incidence of *Staphylococcus aureus* infection has gradually increased. The emergence of meticillin-resistant *S. aureus* (MRSA) is a growing clinical challenge in hospital-associated settings and, more recently, in community settings in the USA and globally [1]. In Taiwan, the prevalence of MRSA infection is approximately 60% of nosocomial *S. aureus* infections [2] and MRSA is also an emerging community-onset pathogen [3].

The impact of the increasing frequency of MRSA bacteraemia is magnified by the poor outcome associated with this serious infection. A growing body of evidence now supports a worse overall outcome for patients with MRSA bacteraemia compared to that for similar patients with meticillin-susceptible *S. aureus* infection [4]. These findings highlight the importance of expedient and aggressive management of MRSA bacteraemia. Repeated *S. aureus* bacteraemia is not uncommon, and the risk is higher for MRSA [5–8], although detailed molecular epidemiology of this clinical entity is limited. A previous report indicated that cases of recurrent *S. aureus* bacteraemia were associated with an indwelling foreign body, with receiving vancomycin therapy, or with haemodialysis dependency [5].

An observational study of 177 patients with MRSA bacteraemia admitted to the emergency department (ED) of National Taiwan University Hospital was conducted from January 2001 to June 2006 [9]. Twenty-eight patients had a history of MRSA bacteraemia prior to the ED visit (inclusion in the study). Among the 118 patients who survived during the hospital stay after inclusion in the study, 24 (20.3%) had repeated MRSA bacteraemia until December 2007. This study investigated the clinical features of patients with repeated MRSA bacteraemia and evaluated the strain-relatedness of MRSA isolates causing

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repeated bacteraemia using pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) analysis.

Materials and Methods

Hospital setting and patient selection

National Taiwan University Hospital (NTUH) is a 2200 bed, academically affiliated medical centre providing both primary and tertiary care in northern Taiwan. This study included all patients aged >16 years with positive *S. aureus* blood cultures within 48 h of arrival at the ED from January 2001 to June 2006. Patients who had been hospitalized for >48 h or who were discharged from any hospital within 48 h were considered to have hospital-onset bacteraemia [10]. Healthcare-associated bacteraemia included bacteraemia related to receiving haemodialysis, chemotherapy or parenteral nutrition on an outpatient basis, nursing home stay, recent surgery or prior hospitalization within 1 year [10]. Bacteraemia in patients without any of the risk factors mentioned above was defined as community-onset bacteraemia.

During the study period, the annual number of ED patient visits was approximately 84 000, and the annual number of positive blood cultures was approximately 1400 (positive rate of blood culture was approximately 17.6%). Among the bacterial isolates from positive blood cultures, 25.2% were Gram-positive bacteria, and *S. aureus* comprised approximately 9.4 % of all isolates. The prevalence of community-onset MRSA bacteraemia is increasing (from 0.009 per 1000 ED visits in 2001 to 0.091 in 2006) [11].

Data collection

The clinical courses and primary sites of bacteraemia were evaluated based on information supplied by primary care physicians and medical records. Data recorded for each patient comprised: age; sex; underlying illness; severity of illness classified by McCabe–Jackson criteria [12]; severity of bacteraemia assessed by the Pittsburg bacteraemia score [13]; installation of a foreign body, including prosthetic joint, pacemaker or intravenous/Foley catheter; debridement, including catheter/foreign body removal or surgical debridement of infected tissue; and metastatic infection, which included documented MRSA infection remote from the original site. Inactive malignancy was not included as an underlying illness. For patients who were not admitted to NTUH, telephone contact was made to collect the required information (four patients were admitted to other hospitals for different reasons after the ED admission). A glycopeptide is the suggested treatment for MRSA infection at our institute, and linezolid is under the control of infectious disease physicians. Early initiation of empirical glycopeptide treatment is not encouraged at our institute [14]. Empirical antimicrobial therapy was defined as adequate when patients received antimicrobial agents active *in vitro* as determined by routine disk susceptibility testing before the notification of MRSA.

Microbiology and antimicrobial susceptibility

Blood culture specimens were inoculated into BACTEC or BACTEC PLUS culture bottles using the BACTEC 9000 system (Becton Dickinson, Sparks, MA, USA). Susceptibilities to antimicrobial agents were determined by the standard disk diffusion method [15]. Subsequent to 2006, a 30-μg cefoxitin disk (BBL Microbiology Systems, Cockeysville, MD, USA) has been applied to detect MRSA [16]. Clinical isolates of MRSA

TABLE 1. Comparison of 28 patients with meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia prior to visits to the emergency department and 149 patients without prior MRSA bacteraemia

Variables	Without prior MRSA bacteraemia (n = 149)	With prior MRSA bacteraemia (n = 28)
Age	66.3 ± 16.0	63.0 ± 17.1
Sex (male/female)	86/63	19/9
Source of patients		
Community	21 (14.1)	0 (0)
Healthcare	110 (73.8)	24 (85.7)
Nosocomial	18 (12.1)	4 (14.3)
McCabe classification		
Rapidly fatal disease	12 (8.0)	1 (3.6)
Ultimately fatal disease	73 (49.0)	20 (71.4)
Nonfatal disease	64 (43.0)	7 (25.0)
Foreign body	66 (44.3)	12 (42.9)
Debridement	58 (38.9)	11 (39.3)
Pittsburg bacteraemia Score	3.5 ± 3.2	3.9 ± 3.6
Adequate empirical antimicrobial therapy	18 (12.1)	11 (39.3)*
Underlying illness		
Diabetes mellitus	56 (37.6)	9 (32.1)
End-stage renal disease	33 (22.1)	11 (39.3)
Heart disease	31 (20.8)	7 (25.0)
Stroke	36 (24.2)	5 (17.9)
Active malignancy	32 (21.5)	3 (10.7)
Liver cirrhosis	9 (6.0)	4 (14.3)
Intravenous drug user	4 (2.7)	0 (0)
Predisposing factors		
Arterio-venous fistula/graft	21 (14.1)	8 (28.6)
Catheter use	47 (31.5)	8 (28.6)
Double lumen catheter	16 (10.7)	5 (17.9)
Port-A catheter	16 (10.7)	1 (3.6)
Perm-cath	11 (7.4)	1 (3.6)
Central venous catheter	5 (3.4)	1 (3.6)
Foley	17 (11.4)	1 (3.6)
Type of infection		
Catheter related	34 (22.8)	6 (21.4)
Soft tissue infection	31 (20.8)	6 (21.4)
Primary bacteraemia	20 (13.4)	7 (25.0)
Orthopedic infection	15 (10.1)	1 (3.6)
Infective endocarditis	9 (6.0)	3 (10.7)
Respiratory tract infection	22 (14.8)	2 (7.1)
Endovascular infection other than infective endocarditis	6 (4.0)	3 (10.7)
Urinary tract infection	10 (6.7)	0 (0)
Biliary tract infection	2 (1.3)	0 (0)
Metastatic infection	17 (11.4)	6 (21.4)
In-hospital mortality	48 (32.2)	11 (39.3)

*p <0.05

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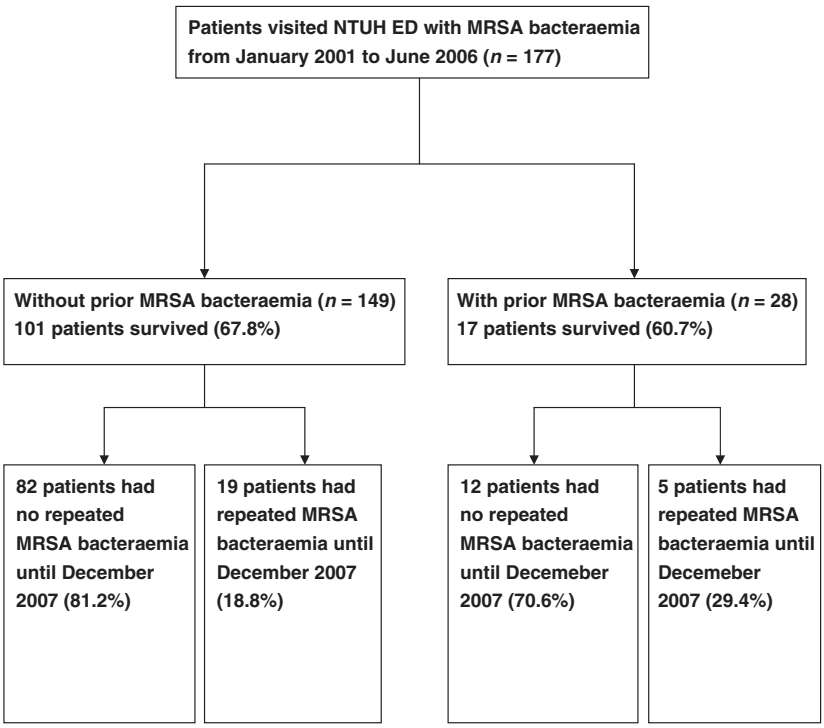

FIG. 1. The distribution of 177 patients presented to National Taiwan University Hospital emergency department (NTUHED) with methicillan-resistant *Staphylococcus aureus* (MRSA) bacteraemia from January 2001 to June 2006. Until December 2007, patients had reported MRSA bacteraemia.

were collected and stored at −70°C in trypticase soy broth (Difco Laboratories, Detroit, MI, USA) supplemented with 15% glycerol.

Definition of clinical status

Infective endocarditis (IE) was defined according to the modified Duke criteria [17]; catheter-related bacteraemia was defined as a positive semiquantitative tip culture (≥15 CFU) and/or high clinical suspicion; pneumonia was defined as a MRSA-positive culture from purulent sputum samples and the presence of newly-developed lung infiltrates; urinary tract infection was defined as a positive urine culture and pyuria; orthopaedic infections included osteomyelitis documented by pathology or imaging study with compatible clinical findings, prosthetic joint infection or septic arthritis and/or positive microbiological results obtained according to current suggestions [18]; and soft tissue infection was defined as clinical soft tissue inflammation plus bacteraemia. If no primary focus could be identified, the bacteraemia was classified as primary. Routine decolonization of MRSA was not performed in our hospital. Repeated bacteraemia within 28 days of discontinuing antimicrobial agent was considered as incomplete treatment.

PFGE and MLST

PFGE was performed on available repeated isolates from MRSA bacteraemia. The details of the method used to perform PFGE were described in our previous study [19]. For restriction endonuclease digestion of the DNA plug, *Sma*I (New England Biolabs, Beverly, MA, USA) was used for MRSA isolates. Other procedures were the same as those described in our previous study [19]. The PFGE results were analysed with Gelcompar for Windows, Version 3.1 (Applied Math, Kortrijk, Belgium). Those differing by ≦three bands were considered to be closely-related strains [20]. Moreover, MLST was performed on these isolates [19], but isolates with same MLST have not to be considered closely-related.

Statistical analysis

The mean and standard deviation were calculated for continuous variables. Percentage was used for categorical variables. Student's *t*-test was used for comparison of continuous variables. Categorical variables were analysed by chi squared or Fisher's exact test. An univariate analysis for risk factors of repeated bacteraemia was performed among patients surviving the index hospitalization. Patients with a history of MRSA bacteraemia prior to index hospitalization were excluded. Factors associated with repeated bacteraemia on univariate analysis ($p < 0.1$) were further evaluated with multivariate logistic regression with forward selection. ORs and the corresponding 95% CIs were calculated. Data were collected in a Microsoft Excel database (Microsoft Excel 2001; Microsoft Corp., Seattle, WA, USA) and analysed with SPSS software for Windows release 10.0 (SPSS Inc., Chicago, IL, USA).

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Results

From January 2000 to June 2006, a total of 177 patients with MRSA bacteraemia were identified, of whom patients with healthcare-associated MRSA bacteraemia comprised 75.7%. Among the 177 patients, 59 (33.3%) patients died during the index hospitalization. Twenty-eight of these patients had previous episodes of MRSA bacteraemia before inclusion in the study and 11 (39.3%) of them died. The comparison between patients with and those without prior MRSA bacteraemia showed no obvious differences, except that patients in the group with prior MRSA bacteraemia received a higher percentage of adequate empirical antimicrobial therapy (Table 1). Among the remaining 118 patients, 24 developed repeated MRSA bacteraemia after inclusion in the study (Fig. 1).

Patients with repeated bacteraemia

The comparisons of clinical characteristics of the 82 patients with single episode of MRSA bacteraemia and the 24 patients with repeated bacteraemia after the index hospitalizations are summarized in Table 2. Twelve patients with a history of MRSA bacteraemia, but with no repeated bacteraemia after inclusion, were excluded (Fig. 1). The mean age of the 24 patients with repeated MRSA bacteraemia was 60 years and 14 (58.3%) of them were men. Healthcare-associated bacteraemia was the most common (91.7%) form and no community-onset bacteraemia was identified in this group. Five of them had a history of prior MRSA bacteraemia (two had end-stage renal disease, two had active malignancy, and one was an intravenous drug user). Forty-six per cent of patients had a foreign body in place at the time of bacteraemia onset. End-stage renal disease was the most common underlying disease, followed by diabetes mellitus, heart disease and

TABLE 2. Comparison of 24 patients with repeated meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia after visits to the emergency department and 82 patients without repeated MRSA bacteraemia

Variables	Nonrepeated bacteraemia (*n* = 82)	Repeated bacteraemia (*n* = 24)	Odds ratio	95% CI	p value
Age	64.3 ± 16.6	60.0 ± 17.1	0.99	0.96–1.01	0.276
Sex (male/female)	47/35	14/10	1.04	0.41–2.62	0.929
Source of patients					
Community	16 (19.5)	0 (0)	–	–	–
Healthcare	59 (72.0)	22 (91.7)	4.29	0.93–19.72	0.061
Nosocomial	7 (8.5)	2 (8.3)	–	–	–
McCabe classification					
Rapidly fatal disease	1 (1.2)	1 (4.2)	–	–	–
Ultimately fatal disease	33 (40.2)	18 (75.0)	4.45	1.60–12.40	0.004
Nonfatal disease	48 (58.5)	5 (20.8)	–	–	–
Foreign body	32 (39.0)	11 (45.8)	1.85	0.74–4.62	0.190
Debridement	38 (46.3)	12 (50.0)	1.16	0.47–2.88	0.752
Pittsburg Bacteraemia Score	2.3 ± 2.1	2.8 ± 2.1	1.09	0.89–1.34	0.388
Adequate empirical antimicrobial therapy	7 (8.5)	8 (33.3)	5.36	1.70–16.90	0.004
Duration of treatment	30.6 ± 29.8	31.3 ± 21.3	1.00	0.98–1.02	0.919
Underlying illness					
Diabetes mellitus	28 (34.1)	8 (33.3)	0.96	0.37–2.53	0.941
End-stage renal disease	17 (20.7)	11 (45.8)	3.24	1.23–8.49	0.017
Heart disease	13 (15.9)	7 (29.2)	2.19	0.76–6.32	0.149
Stroke	20 (24.4)	3 (12.5)	0.44	0.12–1.64	0.223
Active malignancy	10 (12.2)	7 (29.2)	2.96	0.99–8.92	0.053
Liver cirrhosis	5 (6.1)	2 (8.3)	2.96	0.25–7.72	0.699
Intravenous drug user	2 (2.4)	2 (8.3)	3.64	0.48–27.30	0.209
Predisposing factors					
Arterio-venous fistula/graft	12 (14.6)	8 (33.3)	2.92	1.02–8.31	0.045
Catheter use	22 (26.8)	10 (41.7)	1.95	0.76–5.02	0.168
Double lumen catheter	8 (9.8)	5 (20.8)	2.43	0.71–8.29	0.155
Port-A catheter	7 (8.5)	2 (8.3)	0.97	0.19–5.03	0.975
Perm-cath	4 (4.9)	3 (12.5)	2.79	0.58–13.42	0.202
Central venous catheter	3 (3.7)	0 (0)	–	–	–
Foley	8 (9.8)	0 (0)	–	–	–
Type of infection					
Catheter related	17 (20.7)	8 (33.3)	1.91	0.70–5.21	0.205
Soft tissue infection	20 (24.4)	4 (16.7)	0.62	0.19–2.03	0.430
Primary bacteraemia	10 (12.2)	3 (12.5)	1.03	0.26–4.08	0.968
Orthopedic infection	14 (17.1)	1 (4.2)	0.21	0.03–1.70	0.143
Infective endocarditis	1 (1.2)	5 (20.8)	21.32	2.35–193.22	0.007
Respiratory tract infection	7 (8.5)	2 (8.3)	0.97	0.19–5.03	0.975
Endovascular infection other than infective endocarditis	4 (4.9)	0 (0)	–	–	–
Urinary tract infection	7 (8.5)	1 (4.2)	0.07	0.01–0.68	0.021
Biliary tract infection	2 (2.4)	0 (0)	–	–	–
Metastatic infection	6 (7.3)	4 (16.7)	2.53	0.65–9.85	0.180

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stroke. Catheter-related bacteraemia was the most common type of infection (33.3%), followed by infective endocarditis (20.8%), soft tissue infection (16.7%) and primary bacteraemia (12.5%). The duration from discontinuation of therapy to repeated episodes was in the range 35–854 days (median 86 days). Eight patients (33.3%) died during the second episode of MRSA bacteraemia.

Comparison of patients with single and repeated bacteraemia

Patients with repeated MRSA bacteraemia were more likely to have ultimately fatal disease, received adequate empirical antimicrobial therapy, end-stage renal disease, active malignancy, arterio-venous fistula/graft and infective endocarditis (Table 2). Patients with urinary tract infection had less repeated bacteraemia. The duration of treatment and severity of bacteraemia were not significant factors for repeated bacteraemia. Multivariate analysis showed a diagnosis of infective endocarditis (OR 26.09, 95% CI 2.51–270.77, p 0.006) and active malignancy (OR 5.10, 95% CI 1.47–17.68, p 0.01) were significant predictors of recurrent MRSA bacteraemia. End-stage renal disease (OD 3.00, 95% CI 0.90–9.99, p 0.07) was of borderline significance.

PFGE of isolates of repeated MRSA bacteraemia

Among the 24 patients with repeated bacteraemia after index ED visits, 15 patients had available isolates (15 pairs of isolates) for PFGE analysis. Among the 15 pairs of repeated isolates, 13 (86.7%) were closely-related (Fig. 2). ST239 was the most common genotype (20 isolates), followed by ST59 (five isolates) and ST149 (three isolates). Among the 28 patients with prior MRSA bacteraemia before index ED visit, 17 patients had available previous MRSA isolates (17 pairs of isolates) and 16 (94.1%) of them were closely-related (Fig. 3). ST239 was again the most common genotype (17 isolates), followed by ST149 (six isolates), ST59 (four isolates) and ST573 (two isolates). In total, 29 (90.6%) of the 32 pairs of MRSA isolates causing repeated bacteraemia were identified as genetically closely-related strains.

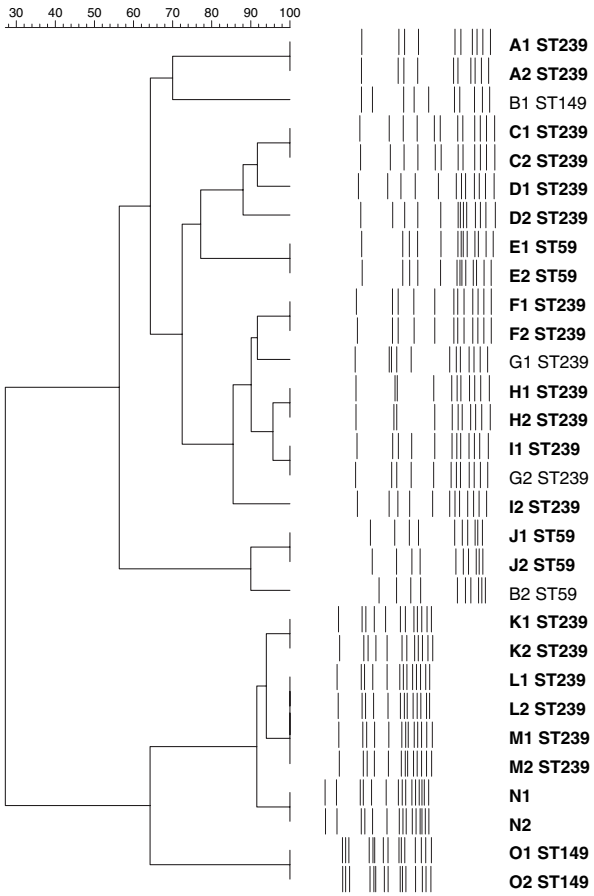

FIG. 2. Pulsed-field gel electrophoresis patterns of isolates recovered from 15 patients (patients A to O) with repeated meticillin-resistant *Staphylococcus aureus* bacteraemia after visits to the emergency department (1, original isolate; 2, repeat isolates).

Discussion

Recurrence is an important concern in patients with *S. aureus* bacteraemia, especially for MRSA. Fowler *et al.* [5] reported that 82.1% of recurrent *S. aureus* bacteraemia cases were the result of PFGE confirmed relapse. In the present study, similar PFGE patterns to previous isolates were found in 90.6% of the isolates of patients with repeated MRSA bacteraemia. These findings might imply incomplete treatment for occult focus or persistent carriage of the same strain.

Fowler *et al.* [5] found that 86% of patients with recurrent *S. aureus* bacteraemia developed a second episode within 90 days of their initial infection. However, in the present study, the duration from discontinuation of therapy to recurrence was in the range 35–854 days (median 86 days) and only half of the patients developed the second episode of MRSA bacteraemia within 90 days. This variation in second episode timing is so large that clinicians should be alert to the possibility of repeated MRSA bacteraemia even months after the initial episode.

Previous studies showed infective endocarditis was a risk factor for recurrence of *S. aureus* bacteraemia [21] and difficult to treat [22]. The present study confirmed that IE was significantly associated with recurrent MRSA bacteraemia. In our hospital, transoesophageal echocardiography was not routinely performed for patients with MRSA bacteraemia.

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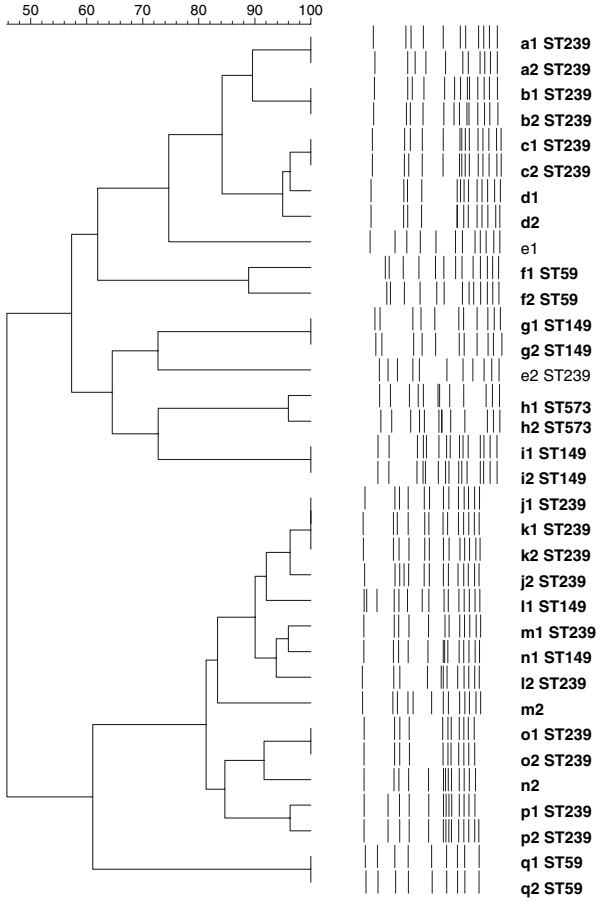

FIG. 3. Pulsed-field gel electrophoresis patterns of isolates recovered from 17 patients (patients a to q) with repeated meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia who had prior nosocomial MRSA bacteraemia isolates prior to visits to the emergency department (ED) and isolates after ED visits (1, prior isolate; 2, isolate obtained in this study).

Thus, an under-diagnosis of IE [23] might explain why only five patients with repeated MRSA bacteraemia had an IE diagnosis in the present study. The present study indicates that the current recommendation to perform transoesophageal echocardiography for all patients with MRSA bacteraemia should be applied more strictly [24]. Active malignancy was significantly associated with repeated MRSA bacteraemia in this study. Among the seven patients with both malignancy and repeated bacteraemia, four had intravascular catheters. Our findings reveal that the risk factors for repeated MRSA bacteraemia included the use of intravascular catheters, an immunocompromised condition, and frequent hospital visits and interventions [25]. Previous studies also found that end-stage renal disease was significantly associated with increased MRSA bacteraemia [26] and repeated bacteraemia [5]. The causes of MRSA bacteraemia in these patients were similar to those found in patients with malignancy, as well as those related to the existence of a foreign body and repeated medical interventions.

A study by Huang *et al.* [6] suggested that most repeated MRSA infections were caused by same strain, and that a single successful decolonization may prevent the majority of later MRSA infection. The present study provided similar findings in that most isolates from patients with repeated MRSA bacteraemia showed close genetic relatedness. However, the effect of decolonization remains controversial, most likely as a result of the extensive nature of the sites that MRSA could colonize and the limited methods available to eradicate MRSA [27]. Moreover, Pena *et al.* [28] demonstrated that, in patients on haemodialysis receiving mupirocin for decolonization of MRSA nasal carriage, 43.5% had nasal recurrence, and 70% of them were considered as relapsed according to PFGE results. Regular nasal swabs for MRSA were not routinely performed during the present study, and related data are required in patients with MRSA bacteraemia to determine whether a more direct relationship exists between colonization and invasive infections.

In the present study, although patients with repeated bacteraemia were more likely to receive adequate empirical antimicrobial treatment, they still showed higher mortality and recurrence. The explanation of higher possibility of adequate empirical therapy in patients with repeated bacteraemia centres on patients' underlying illness, especially end-stage renal disease and active malignancy, which might encourage aggressive empirical therapy. The effectiveness of empirical glycopeptides on patient outcome has been controversial [14,29,30]. In our previous study [9], we showed that the severity of underlying illness, and the severity of bacteraemia and persistent bacteraemia, were correlated with mortality, and not with empirical therapy. On the other hand, we maintain that empirical therapy is not a major factor for recurrence. The completeness of adequate target therapy is more important. However, although prolonged treatment has been suggested for MRSA bacteraemia [31], the duration of treatment is not a significant factor for recurrence in the present study, in accordance with a previous report by Kreisel *et al.* [8].

The present study has several limitations. First, the possibility of incomplete treatment or any occult focus could not be excluded despite the fact that half of our patients had repeated infection at least 3 months later, which is longer than the suggested observation period for *S. aureus* bacteraemia. Second, most of our cases were healthcare-associated MRSA strains. The genotype analyses showed that the most common isolate was ST239, which was the most prevalent healthcare-associated strain in Taiwan [19]. However, there were still a few ST59 strains (SCCmec IV or V) among patients with repeated bacteraemia, which were common

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community-onset MRSA strains [11], although none of the patients were considered as having true community-onset MRSA bacteraemia. This might only reflect that ST59 is replacing ST239 as healthcare-related strain. Because of geographic differences, the results obtained in the present stusy can not be generalized to other settings. Third, because we did not perform environmental cultures, the contribution of a patient's immediate surroundings to maintaining carriage with the same strain could not be assessed [6].

In conclusion, repeated MRSA bacteraemia is common and carries a high mortality rate. Most cases were recurrent infections caused by the same strains. Clinical characteristics associated with repeated bacteraemia included a diagnosis of infective endocarditis and active malignancy.

Transparency Declaration

The authors declare no conflict of interests.

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